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The application was originally filed in English.

(71) Sökande Astra Pharmaceuticals Ltd, Kings Langley GB
Applicant (s)

(21) Patentansökningsnummer 9702773-4
Patent application number

(86) Ingivningsdatum 1997-07-22
Date of filing

Stockholm, 1998-08-03

För Patent- och registreringsverket
For the Patent- and Registration Office

Evy Morin
Evy Morin

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NOVEL COMPOUNDS

The present invention provides new triazolo[4,5-*d*]pyrimidine compounds, their use as medicaments, compositions containing them and processes for their preparation.

5 Platelet adhesion and aggregation are initiating events in arterial thrombosis. Although the process of platelet adhesion to the sub-endothelial surface may have an important role to play in the repair of damaged vessel walls, the platelet aggregation that this initiates can precipitate acute thrombotic occlusion of vital vascular beds, leading to events with high morbidity such as myocardial infarction and unstable angina. The success of interventions used to prevent or alleviate these conditions, such as thrombolysis and angioplasty is also compromised by platelet mediated occlusion or re-occlusion.

15 A number of converging pathways lead to platelet aggregation. Whatever the initial stimulus, the final common event is a cross linking of platelets by binding of fibrinogen to a membrane binding site, glycoprotein IIb/IIIa (GPIIb/IIIa). The high anti-platelet efficacy of antibodies or antagonists for GPIIb/IIIa is explained by their interference with this final common event. However, this efficacy may also explain the bleeding problems that have been observed with this class of agent. Thrombin can produce platelet aggregation largely independently of other pathways but substantial quantities of thrombin are unlikely to be present without prior activation of platelets by other mechanisms. Thrombin inhibitors such as hirudin are highly effective anti-thrombotic agents, but again may produce excessive bleeding because they function as both anti-platelet and anti-coagulant agents (The TIMI 9a Investigators (1994), *Circulation* **90**, pp. 1624-1630; The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators (1994) *Circulation* **90**, pp. 1631-1637; Neuhaus K.L. et. al. (1994) *Circulation* **90**, pp.1638-1642).

30 It has been found that ADP acts as a key mediator of thrombosis. A pivotal role for ADP is supported by the fact that other agents, such as adrenaline and 5-hydroxytryptamine (5HT, serotonin) will only produce aggregation in the presence of ADP. The limited anti-thrombotic efficacy of aspirin may reflect the fact that it blocks only one source of ADP which is that released in a thromboxane-dependent manner following platelet adhesion (see e.g. Antiplatelet Trialists' Collaboration (1994), *Br. Med. J.* **308**, pp. 81-106; Antiplatelet Trialists' Collaboration (1994), *Br. Med. J.* **308**, pp.159-168). Aspirin has no effect on aggregation produced by other sources of ADP, such as damaged cells or ADP released under conditions of turbulent blood flow. ADP-induced platelet aggregation is mediated

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(71) Sökande Astra Pharmaceuticals Ltd, Kings Langley GB
Applicant (s)

(21) Patentansökningsnummer 9702775-9
Patent application number

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Date of filing

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För Patent- och registreringsverket
For the Patent- and Registration Office

Hjordis Segerlund

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It has been found that ADP acts as a key mediator of thrombosis. A pivotal role for ADP is supported by the fact that other agents, such as adrenaline and 5-hydroxytryptamine (5HT, serotonin) will only produce aggregation in the presence of ADP. The limited anti-thrombotic efficacy of aspirin may reflect the fact that it blocks only one source of ADP which is that released in a thromboxane-dependent manner following platelet adhesion (see e.g. Antiplatelet Trialists' Collaboration (1994), *Br. Med. J.* **308**, pp. 81-106; Antiplatelet Trialists' Collaboration (1994), *Br. Med. J.* **308**, pp.159-168). Aspirin has no effect on aggregation produced by other sources of ADP, such as damaged cells or ADP released under conditions of turbulent blood flow. ADP-induced platelet aggregation is mediated

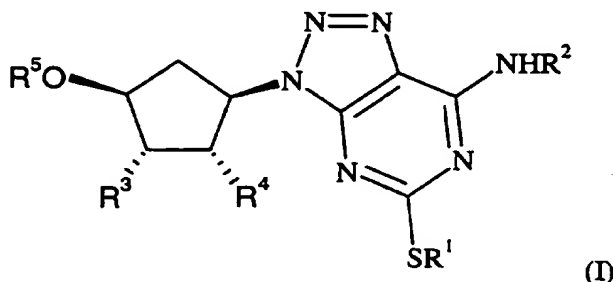
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by the P_{2T} -receptor subtype uniquely located on the platelet membrane. Recently it has been shown that antagonists at this receptor offer significant improvements over other anti-thrombotic agents. Accordingly there is a need to find P_{2T} -antagonists as anti-thrombotic agents.

It has now been found that a series of triazolo[4,5-*d*]pyrimidine derivatives are P_{2T} -receptor antagonists. In a first aspect the invention therefore provides a compound of formula (I):



wherein:

R^1 is a C_{1-6} alkyl, C_{3-8} -cycloalkyl or a phenyl group, each group being optionally substituted by one or more substituents selected from halogen, OR^8 , NR^9R^{10} , SR^{11} or

C_{1-6} alkyl (itself optionally substituted by one or more halogen atoms);

R^2 is C_{1-8} alkyl optionally substituted by one or more substituents selected from halogen, OR^8 , NR^9R^{10} , SR^{11} , C_{3-8} -cycloalkyl, aryl (optionally substituted by one or more alkyl groups and/or halogen atoms), or C_{1-6} -alkyl; or R^2 is a C_{3-8} -cycloalkyl group optionally substituted by one or more substituents selected from halogen, OR^8 , NR^9R^{10} , SR^{11} ,

C_{1-6} -alkyl or phenyl (the latter two groups being optionally substituted by one or more substituents selected from halogen, NO_2 , $C(O)R^8$, OR^8 , SR^{11} , $NR^{12}R^{13}$, phenyl and C_{1-6} -alkyl which is optionally substituted by one or more halogen atoms);

one of R^3 and R^4 is hydroxy and the other is hydrogen, hydroxy or NR^9R^{10} ;

R^5 is hydrogen, C_{1-6} alkyl or $(CH_2)_nR^{14}$ where n is 1 to 3 and R^{14} is $COOH$, OR^{15} , $NR^{16}R^{17}$ or $CONR^{16}R^{17}$;

R^8 , R^9 , R^{10} and R^{11} are independently hydrogen or C_{1-6} alkyl;

R^{12} and R^{13} are independently hydrogen, C_{1-6} alkyl or acyl groups;

R^{15} , R^{16} and R^{17} are independently hydrogen or C_{1-6} alkyl; and

or a pharmaceutically acceptable salt or solvate thereof.

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Alkyl groups, whether alone or as part of another group, can be straight chained or branched.

Suitably R^1 is a C_{1-6} alkyl, C_{3-8} -cycloalkyl or a phenyl group, each group being optionally substituted by one or more substituents selected from halogen, OR^8 , NR^9R^{10} , SR^{11} or C_{1-6} alkyl (itself optionally substituted by one or more halogen atoms). Preferably R^1 is C_{1-8} alkyl. More preferably R^1 is propyl.

Suitably R^2 is C_{1-8} alkyl optionally substituted by one or more substituents selected from halogen, OR^8 , NR^9R^{10} , SR^{11} , C_{3-8} -cycloalkyl, aryl (optionally substituted by one or more alkyl groups and/or halogen atoms), or C_{1-6} -alkyl; or R^2 is a C_{3-8} -cycloalkyl group optionally substituted by one or more substituents selected from halogen, OR^8 , NR^9R^{10} , SR^{11} , C_{1-6} -alkyl or phenyl (the latter two groups being optionally substituted by one or more substituents selected from halogen, NO_2 , $C(O)R^8$, OR^8 , SR^{11} , $NR^{12}R^{13}$, phenyl and C_{1-6} -alkyl which is optionally substituted by one or more halogen atoms) where R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} are as defined above. Aryl groups include phenyl and naphthyl groups. Acyl groups include $C(O)C_{1-6}$ alkyl such as acetyl and 1-oxopropyl. Preferably R^2 is C_{1-6} alkyl or a C_{3-8} -cycloalkyl group optionally substituted by phenyl. More preferably R^2 is butyl or cyclopropyl optionally substituted by phenyl.

Suitably one of R^3 and R^4 is hydroxy and the other is hydrogen or hydroxy or NR^9R^{10} . Preferably R^3 and R^4 are both hydroxy.

Suitably R^5 is hydrogen, C_{1-6} alkyl or $(CH_2)_nR^{14}$ where n is 1 to 3 and R^{14} is $COOH$, OR^{15} , $NR^{16}R^{17}$ or $CONR^{16}R^{17}$ where R^{15} , R^{16} and R^{17} are independently hydrogen or C_{1-6} alkyl. Preferably R^5 is hydrogen or CH_2R^{12} where R^{12} is $COOH$ or $CONH_2$.

Particularly preferred compounds of the invention include:

[1*S*-[1 α ,2 β ,3 β ,4 α (1*S**,2*R**)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentane-1,2,3-triol,

[1*S*-[1 α ,3 β ,4 α (1*S**,2*R**)]]-2-[3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentyl]oxy]acetic acid,

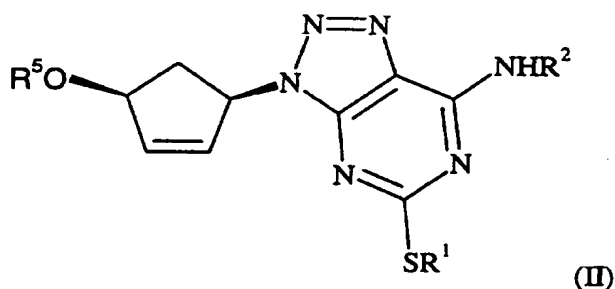
[1*S*-[1 α ,2 β ,4 α (1*S**,2*R**)]]-2-[[2-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentyl]oxy]acetic acid,

[1*S*-(1 α ,2 β ,3 β ,4 α)]-2-[[4-[7-(Butylamino)-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-2,3-dihydroxycyclopentyl]oxy]acetic acid,

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[1*S*-(1 α ,2 β ,3 β ,4 α)]-2-[[4-[7-(Butylamino)-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-2,3-dihydroxycyclopentyl]oxy]acetamide,
or a pharmaceutically acceptable salt or solvate thereof.

- 5 According to the invention there is further provided a process for the preparation of a compound of formula (I) which comprises:
hydroxylation of a compound of formula (II):



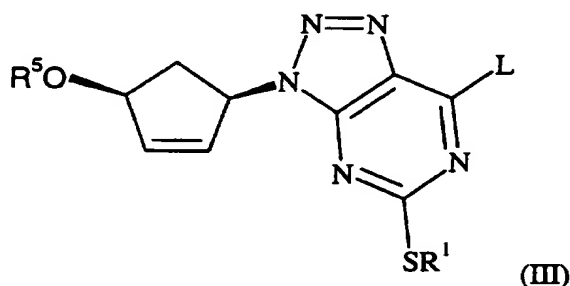
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where R¹, R² and R⁵ are as defined in formula (I) or are protected derivatives thereof,
and optionally thereafter in any order:

- converting one or more functional groups into a further functional groups
- removing any protecting groups
- 15 • forming a pharmaceutically acceptable salt or solvate.

The hydroxylation reaction is carried out using known reagents. For example when R³ and R⁴ are both hydroxy, the reaction can be performed using osmium tetroxide. When one of R³ or R⁴ is hydroxy and the other is hydrogen the reaction can be performed using
20 borane.THF complex.

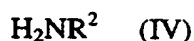
Compounds of formula (II) can be prepared by reacting a compound of formula (III):



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where R^1 and R^5 are as defined in formula (I) or are protected derivatives thereof and L is a leaving group with a compound of formula (IV):



where R^2 is as defined in formula (I) or is a protected derivative thereof. The reaction is carried out in the presence of a base such as a tertiary organic amine in an inert solvent such as dichloromethane at ambient or elevated temperature. Other suitable bases include inorganic bases such as potassium carbonate. Preferred leaving groups include halogen and thioalkyl.

Protecting groups can be added and removed using known reaction conditions. The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

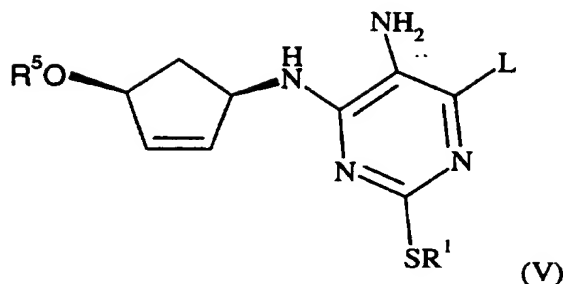
Ester protecting groups can be removed by basic hydrolysis, for example by using a metal hydroxide, preferably an alkali metal hydroxide, such as sodium hydroxide or lithium hydroxide, or quaternary ammonium hydroxide in a solvent, such as aqueous ethanol or aqueous tetrahydrofuran, at a temperature of from 10° to 100°C, preferably the temperature is around room temperature; or by acidic hydrolysis using a mineral acid such as HCl or a strong organic acid such as trichloroacetic acid in a solvent such as aqueous 1,4-dioxane;

Trialkylsilyl protecting groups can be removed by the use of, for example, a fluoride ion source, for example tetra-n-butylammonium fluoride or hydrogen fluoride;

Benzyl groups can be removed by hydrogenolysis using a transition metal catalyst, for example palladium on charcoal, under an atmosphere of hydrogen, at a pressure of from 1 to 5 bar, in a solvent, such as acetic acid.

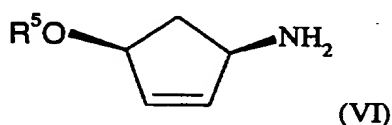
A compound of formula (III) can be prepared by diazotizing of a compound of formula (V):

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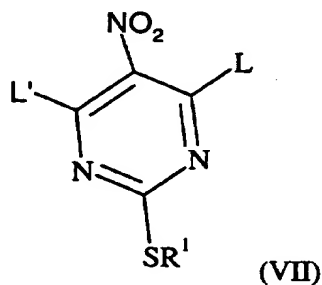


wherein R^1 and R^5 are as defined in formula (I) and L is as defined above with a metal nitrite, for example an alkali metal nitrite, especially sodium nitrite in dilute aqueous acid, for example 2M HCl, or with a C_{1-6} -alkyl nitrite in an inert solvent, at a temperature of from -20 to 100°C . Preferred conditions are isoamyl nitrite in acetonitrile at 80°C .

Compounds of formula (V) are prepared from the corresponding nitro compound, which in turn is prepared by reacting a compound of formula (VI):



in which R^5 is as defined in formula (I) with a compound of formula (VII):



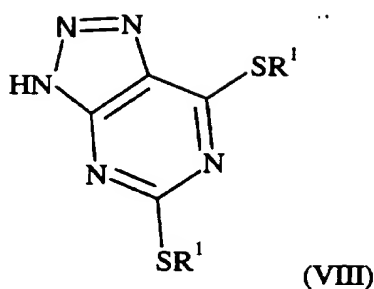
in which R^1 is as defined in formula (I), L is as defined above and L' is a leaving group.

Preferably L and L' are the same and are both chloro. The reaction can be carried out in the presence of a base such as triethylamine in a suitable solvent such as THF.

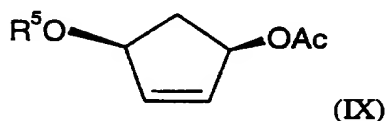
Compounds of formula (III) where L is SR^1 can be prepared by reacting a compound of formula (VIII)

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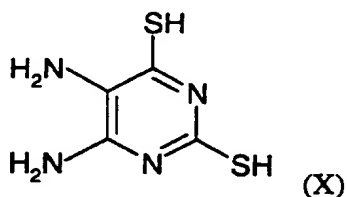


in which R¹ groups are as defined in formula (I) with a compound of formula (IX):



in which R⁵ is as defined in formula (I). The reaction can be carried out in the presence of a suitable transition metal complex, preferably tetrakis(triphenylphosphine) palladium (0).

Compounds of formula (VIII) can be prepared from compounds of formula (X):



by reacting with a compound R¹X where R¹ is as defined in formula (I) and X is a leaving group such as halo, followed by cyclisation.

One or more functional groups in compounds of formula (I) or in intermediate compounds can be converted into further functional groups using standard chemistry. For example a compound where R⁵ is hydrogen can be converted to a compound where R⁵ is CH₂COOH by treating with a compound of formula (XI):



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where R^{18} is C_{1-6} alkyl and X is a leaving group in the presence of a base such as sodium hydroxide followed by hydrolysis of the resulting ester. A compound where R^5 is hydrogen can be converted to a compound where R^5 is C_{1-6} alkyl using standard alkylation conditions. The group SR^1 can be interconverted by oxidation of the sulfur, for example using oxone or MCBPA, followed by treatment with a compound $R^{1'}-SM$ where $R^{1'}$ is a different R^1 group and M is a metal such as sodium.

All novel intermediates form a further aspect of the invention.

Salts of the compounds of formula (I) may be formed by reacting the free acid, or a salt thereof, or the free base, or a salt or a derivative thereof, with one or more equivalents of the appropriate base (for example ammonium hydroxide optionally substituted by C_{1-6} -alkyl or an alkali metal or alkaline earth metal hydroxide) or acid (for example a hydrohalic (especially HCl), sulphuric, oxalic or phosphoric acid). The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. water, ethanol, THF or diethyl ether, which may be removed *in vacuo*, or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin. The non-toxic physiologically acceptable salts are preferred, although other salts may be useful, e.g. in isolating or purifying the product.

The compounds of the invention act as P_{27} -receptor antagonists. Accordingly, the compounds are useful in therapy, especially adjunctive therapy, particularly they are indicated for use as: inhibitors of platelet activation, aggregation and degranulation, anti-thrombotic agents or in the treatment or prophylaxis of unstable angina, coronary angioplasty (PTCA), myocardial infarction, perithrombolysis, primary arterial thrombotic complications of atherosclerosis such as thrombotic or embolic stroke, peripheral vascular disease, myocardial infarction with or without thrombolysis, arterial complications due to interventions in atherosclerotic disease such as angioplasty, endarterectomy, stent placement, coronary and other vascular graft surgery, thrombotic complications of surgical or mechanical damage such as tissue salvage following accidental or surgical trauma, reconstructive surgery including skin and muscle flaps, conditions with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, thrombotic complications of septicaemia, adult respiratory distress syndrome, anti-phospholipid syndrome, heparin-induced thrombocytopenia and pre-eclampsia/eclampsia, or venous thrombosis such as deep vein thrombosis, venoocclusive disease, haematological

conditions such as myeloproliferative disease, including thrombocythaemia; or in the prevention of mechanically-induced platelet activation *in vivo*, such as cardio-pulmonary bypass (prevention of microthromboembolism), mechanically-induced platelet activation *in vitro*, such as use in the preservation of blood products, e.g. platelet concentrates, or shunt occlusion such as in renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis, inflammatory bowel disease and organ graft rejection, conditions such as migraine, Raynaud's phenomenon, atheromatous plaque formation/progression, vascular stenosis/restenosis and asthma, in which platelet-derived factors are implicated in the disease process.

According to the invention there is further provided the use of a compound according to the invention in the manufacture of a medicament for the treatment of the above disorders. The invention also provides a method of treatment of the above disorders which comprises administering to a patient suffering from such a disorder a therapeutically effective amount of a compound according to the invention.

The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by parenteral administration in the form of sterile parenteral solutions or suspensions, by subcutaneous administration, or by rectal administration in the form of suppositories or transdermally.

The compounds of the invention may be administered on their own or as a pharmaceutical composition comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

Dry powder formulations and pressurized HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably finely divided.

The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers include sugars and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, e.g. that known as the Turbuhaler[®] in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound with or without a carrier substance is delivered to the patient.

The pharmaceutical composition comprising the compound of the invention may conveniently be tablets, pills, capsules, syrups, powders or granules for oral administration; sterile parenteral or subcutaneous solutions, suspensions for parenteral administration or suppositories for rectal administration.

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved in either a readily volatile organic solvent or an aqueous solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets, e.g. lactose, saccharose, sorbitol, mannitol, starches, cellulose derivatives or gelatine. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of

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ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

- 5 The invention is illustrated by the following examples. In the examples the NMR spectra were measured on a Varian Unity Inova 300 or 400 spectrometer and the MS spectra were measured as follows: EI spectra were obtained on a VG 70-250S or Finnigan Mat Incos-XL spectrometer, APCI spectra were obtained on Finnigan Mat SSQ7000 or a Micromass Platform spectrometer. Preparative HPLC separations were generally performed using a
10 Novapak[®], Bondapak[®] or Hypersil[®] column packed with BDSC-18 reverse phase silica. Flash chromatography (indicated in the Examples as (SiO₂)) was carried out using Fisher Matrix silica, 35-70 µm.

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Example 1

[1*S*-[1 α ,2 β ,3 β ,4 α (1*S,2*R**)]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentane-1,2,3-triol**

a) [1*S*-*cis*]-4-[[6-Chloro-5-nitro-2-(propylthio)-pyrimidin-4-yl]amino]-2-cyclopentene-1-ol

To a solution of 4,6-dichloro-5-nitro-3-propylthiopyrimidine (prepared as described in WO 9703084) (4.00g) and triethylamine (2.00ml) in dry THF (100ml) was added a solution of [1*S*-*cis*]-4-amino-2-cyclopenten-1-ol (prepared as described by S. F. Martin et al., Tetrahedron Lett., 1992, 33, 3583) (1.48g) in THF /1,4-dioxane 2:1 (150ml) dropwise over 1 hour. The reaction mixture was filtered, concentrated and purified (SiO₂, ethyl acetate:isohexane 1:4 to 1:1 as eluant) to afford the subtitle compound (3.18g). MS (APCI) 313 (M-H₂O+H⁺, 100%)

b)[1*S*-*cis*]-4-[[5-Amino-6-chloro-2-(propylthio)-pyrimidin-4-yl]amino]-2-cyclopentene-1-ol

Iron powder (2.30g) was added to a stirred solution of the product of step (a) (2.61g) in acetic acid (100ml). The reaction mixture was stirred at room temperature for 2 hours, concentrated to half volume, diluted with ethyl acetate and washed with water. The organic phase was dried and concentrated to afford the subtitle compound (2.28g). NMR δ H (d₆-DMSO) 7.03 (1H, d), 5.93-5.90 (1H, m), 5.85-5.82 (1H, m), 5.05 (1H, d), 4.91-4.85 (2H, m), 4.66-4.60 (1H, m), 2.94 (2H, t), 2.77-2.68 (1H, m), 1.69-1.57 (2H, sextuplet), 1.48-1.42 (1H, quintuplet), 0.94 (3H, t).

c)[1*S*-*cis*]-4-[7-Chloro-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-2-cyclopentene-1-ol

Isoamyl nitrite (1.08ml) was added to a solution of the product of step (b) (2.20g) in acetonitrile (100ml) and the solution heated at 70°C for 1 hour. The cooled reaction mixture was concentrated and purified (SiO₂, ethyl acetate:isohexane 1:2 as eluant) to afford the subtitle compound (1.79g). MS (APCI) 312 (M+H⁺), 224 (100%)

d) [1*R*-*trans*]-*N*-[(2,4-Dimethoxyphenyl)methyl]-2-phenyl-cyclopropanamine

A solution of (1*R*-*trans*)-2-phenyl-cyclopropanamine, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L.A. Mitscher et al., J. Med. Chem.

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1986, 29, 2044) (1.92g) in 1N aqueous NaOH (50ml) was stirred for 10 minutes and extracted with dichloromethane. The extract was dried, evaporated and the residue was dissolved in methanol (30ml). To this was added 2,4-dimethoxybenzaldehyde (1.12g) and the pH adjusted to 5 with acetic acid. Sodium cyanoborohydride (0.46g) was added. The mixture was stirred overnight, basified with 2N NaOH and extracted with ethyl acetate. The extract was dried, evaporated and purified (SiO₂, methanol:dichloromethane: 0.880 ammonia 2: 98: 0.1 as eluant) to afford the subtitle compound (1.10g). NMR δ H (CDCl₃) 7.23-6.97 (6H, m), 6.49-6.41 (2H, m), 3.73 (3H, s), 3.69 (3H, s), 3.66 (2H, s), 2.21-2.16 (1H, m), 1.82-1.76 (1H, m), 1.01-0.87 (2H, m).

e) [1S-[1 α ,4 α (1S*,2R*)]]-4-[7-[N-[(2,4-Dimethoxyphenyl)methyl]-(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-2-cyclopentene-1-ol

A solution of the product from step (c) (0.73g), the product from step (d) (0.73g) and *N,N*-diisopropylethylamine (815 μ l) in 1,4-dioxane (25ml) was stirred at room temperature for 1 hour. The reaction mixture was concentrated and the residue purified (SiO₂, ethyl acetate: hexane 1:2 as eluant) to afford the subtitle compound (1.18g).

MS (APCI) 559 (M+H⁺, 100%)

f) [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-4-[7-[N-[(2,4-Dimethoxyphenyl)methyl]-(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentane-1,2,3-triol

To a solution of the product of step (e) (0.50g) in acetone (10ml) and water (7ml) was added *N*-methylmorpholine-*N*-oxide (0.38g) followed by osmium tetroxide (390 μ l, 2.5% solution in *t*-butanol). The mixture was stirred at room temperature overnight and treated with sodium hydrosulphite (0.90g). The suspension was filtered through celite and the product purified (SiO₂, ethyl acetate: hexane 1:1 as eluant) to afford the subtitle compound (0.22g).

MS (APCI) 593 (M+H⁺, 100%)

g) [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-4-[7-[2-(Phenylcyclopropyl)amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentane-1,2,3-triol

A solution of the product from step (f) (0.22g) in trifluoroacetic acid (9ml)/water (1ml) was stirred overnight. The mixture was concentrated, neutralised with 1N aqueous NaOH and suspended in acetonitrile/water. The suspension was filtered and the filtrate purified

(HPLC, Novapak® C18 column, 0.1% aqueous ammonium acetate:acetonitrile, 60:40) to afford the title compound (0.12g).

MS (APCI) 443 (M+H⁺, 100%)

NMR δH (d₆-DMSO) (Rotamers) 7.29 (2H, m), 7.16 (3H, m), 5.11-4.91 (3H, 3xbr s), 4.97 (1H, q), 4.67 (1H, m), 3.93 (1H, br s), 3.78 (1H, m), 3.22 (1H, quintet), 2.95-2.81 (2H, m), 2.58 (1H, m), 2.13 (1H, m), 1.91 (1H, m), 1.51 (3H, m), 1.31 (1H, m), 0.81 (3H, t).

Example 2

[1S-[1α,3β,4α(1S*,2R*)]]-2-[3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-cyclopentyl]oxy]acetic acid, hemiammonium salt

a) [1S-[1α,4α(1S*,2R*)]]-2-[[4-[7-[N-[(2,4-Dimethoxyphenyl)methyl]-(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-cyclopentyl]oxy]acetic acid, 1,1-dimethylethyl ester

To a solution of the product from example 1 step (e) (1.20g) in toluene (10ml) was added aqueous NaOH (5N, 10ml) followed by tetrabutylammonium bromide (0.10g) and the mixture stirred for 30 minutes. Dimethyl sulfoxide (670μl) and *tert*-butyl bromoacetate (3.47ml) were added and the reaction mixture stirred for 1 hour. The organic phase was washed with water and brine, dried and evaporated. The residue was purified (SiO₂, ethyl acetate: hexane 15:85 to 3:7 as eluant) to afford the subtitle compound (0.96g).

MS (APCI) 673 (M+H⁺, 100%)

b) [1S-[1α,3β,4α(1S*,2R*)]]-2-[[4-[7-[N-[(2,4-Dimethoxyphenyl)methyl]-(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-3-hydroxycyclopentyl]oxy]acetic acid, 1,1-dimethylethyl ester and [1S-[1α,2β,4α(1S*,2R*)]]-2-[[4-[7-[N-[(2,4-Dimethoxyphenyl)methyl]-(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-2-hydroxycyclopentyl]oxy]acetic acid, 1,1-dimethylethyl ester

A solution of the product from step (a) (1.08g) in tetrahydrofuran (15ml) at 0°C was treated with borane-tetrahydrofuran complex (1M solution in tetrahydrofuran, 8.02ml) dropwise. The reaction mixture was stirred at 0°C for 16 hours. Methanol was added and the mixture was stirred at room temperature and then concentrated. The residue was dissolved in diglyme (10ml) then treated with trimethylamine-*N*-oxide (0.48g). The reaction mixture was heated at 130°C for 2 hours then diluted with ethyl acetate and washed with brine, 1N

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HCl and aqueous sodium bicarbonate, dried and concentrated. Purification (SiO₂, ethyl acetate: hexane 3:7 as eluant) gave the two products:

(i) [1*S*-[1 α ,3 β ,4 α (1*S**,2*R**)]]-2-[[4-[7-[*N*-[(2,4-Dimethoxyphenyl)methyl]-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-3-hydroxycyclopentyl]oxy]acetic acid, 1,1-dimethylethyl ester (0.33g)
NMR δ H (d₆-DMSO) 7.27-7.11 (5H, m), 6.98 (1H, d), 6.54 (1H, d), 6.39 (1H, m), 5.23 (2H, br m), 5.03 (1H, d), 4.80 (3H, m), 4.20 (1H, m), 3.95 (2H, s), 3.71 (3H, s), 3.66 (3H, s), 3.00-2.90 (3H, m), 2.65 (1H, m), 2.38 (1H, br m), 2.30-2.10 (2H, m), 1.95 (1H, m), 1.60 (2H, sextuplet), 1.45 (1H, m), 1.43 (9H, s), 0.90 (3H, t).

(ii) [1*S*-[1 α ,2 β ,4 α (1*S**,2*R**)]]-2-[[4-[7-[*N*-[(2,4-Dimethoxyphenyl)methyl]-(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-2-hydroxycyclopentyl]oxy]acetic acid, 1,1-dimethylethyl ester (0.21g)
NMR δ H (d₆-DMSO) 7.27-7.11 (5H, m), 6.98 (1H, d), 6.54 (1H, d), 6.40-6.36 (1H, m), 5.27 (2H, m), 4.89 (1H, d), 4.25 (1H, m), 4.04 (2H, s), 3.88 (1H, m), 3.71 (3H, s), 3.65 (3H, s), 3.00-2.90 (3H, m), 2.67 (1H, m), 2.37 (1H, m), 2.30-2.10 (2H, m), 1.61 (2H, sextuplet), 1.44 (1H, m), 1.43 (9H, s), 0.91 (3H, t).

c) [1*S*-[1 α ,3 β ,4 α (1*S**,2*R**)]]-2-[[3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentyl]oxy]acetic acid, hemiammonium salt

The title compound was prepared according to the method of example 1 step (g) using the product of step (b)(i).

MS (APCI) 485 (M+H⁺, 100%)
NMR δ H (d₆-DMSO) 7.31-7.15 (5H, m), 4.78-4.68 (2H, m), 4.17 (1H, m), 3.90 (2H, s), 3.20 (1H, m), 2.97-2.81 (2H, m), 2.65-2.52 (1H, m), 2.25-2.11 (3H, m), 1.92-1.85 (1H, m), 1.55-1.45 (3H, m), 1.34 (1H, m), 0.81 (3H, t).

Example 3

[1*S*-[1 α ,2 β ,4 α (1*S**,2*R**)]]-2-[[2-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentyl]oxy]acetic acid, hemiammonium salt

The title compound was prepared according to the method of example 1 step (g) using the product of step (b)(ii).

MS (APCI) 485 (M+H⁺, 100%)

NMR δ H (d_6 -DMSO) 7.31-7.16 (5H, m), 5.21 (1H, quintet), 4.28 (1H, m), 4.03-3.92 (2H, m), 3.82 (1H, m), 3.19 (1H, m), 2.96-2.83 (2H, m), 2.64 (1H, m), 2.41 (1H, m), 2.16-2.08 (3H, m), 1.54-1.47 (3H, m), 1.33 (1H, m), 0.82 (3H, t).

5 **Example 4**

[1S-(1 α ,2 β ,3 β ,4 α)]-2-[[4-[7-(Butylamino)-5-(propylthio)-3H-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-2,3-dihydroxycyclopentyl]oxy]acetic acid

a) **5,7-Bis(propylthio)-1H-1,2,3-triazolo[4,5-*d*]pyrimidine**

10 A mixture of 4,5-diamino-2,6-dimercaptopyrimidine (25g), potassium hydroxide (36.9g) and propyl iodide (62.9ml) in water (710ml) was stirred for 72 hours. The product was collected by filtration, washed with water and dried. The material was taken into water (710ml)/glacial acetic acid (710ml), cooled to 5°C and a solution of sodium nitrite (9.38g) in water (109ml) added, maintaining the temperature below 5°C. The mixture was allowed
15 to reach room temperature and the product was collected by filtration, washed with water and dried (28.9g).

MS (EI) 269 (M^+)

b) **Mixture of (1S-*cis*)-4-[5,7-bis(propylthio)-3H-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-2-cyclopentene-1-ol and (1S-*cis*)-4-[5,7-bis(propylthio)-2H-1,2,3-triazolo[4,5-*d*]pyrimidin-2-yl]-2-cyclopentene-1-ol**

To a solution of the product from step (a) (3.7g), (1S-*cis*)-4-acetoxy-2-cyclopenten-1-ol (2.0g) and triethylamine (6ml) in THF (100ml) at 60°C was added tetrakis(triphenylphosphine)palladium (0) (2.0g), as a suspension in THF (50ml). The
25 reaction mixture was stirred at 60°C for 4.5 hours and purified (SiO_2 , ethyl acetate: hexane 1:3 as eluant) to give the product as a 2:1 isomeric mixture.

MS (APCI) 352 ($M+H^+$, 100%)

c) **[3aR-(3 α ,4 α ,6 α ,6 α)]-6-[5,7-Bis(propylthio)-3H-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol**

30 A mixture of the product from step (b) (2.0g), 4-methylmorpholine-*N*-oxide (1.27g) and osmium tetroxide (2.5% solution in *tert*-butanol, 2.9ml) in acetone (110ml) and water (25ml) was stirred at room temperature for 16 hours. Sodium hydrosulfite (2.0g) was added and the mixture was stirred for 1 hour then filtered through celite, washing with ethyl
35 acetate. The combined filtrates were concentrated and the residue dissolved in acetone (75ml). Tosic acid (1.08g) and 1,1-dimethoxypropane (6ml) were added and the mixture

was stirred for 1 hour. The solution was concentrated and the residue was partitioned between dichloromethane and water. The organic phase was dried and concentrated and the residue purified (SiO₂, ethyl acetate: hexane 1:4 as eluant) to give the subtitle compound (1.08g).

5 MS (APCI) 426 (M+H⁺, 100%)

d) [3aR-(3α,4α,6α,6α)]-2-[[6-[5,7-Bis(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]oxy]acetic acid, 1,1-dimethylethyl ester

10 To a solution of the product from step (c) (0.36g) in THF (10ml) at 0°C was added sodium hydride (60% in oil, 37mg). The mixture was stirred at 0°C for 15 minutes and *tert*-butyl bromoacetate (0.137ml) was added. The mixture was stirred at room temperature for 24 hours and purified (SiO₂, ethyl acetate: hexane 1:10 as eluant) to give the subtitle compound (0.16g).

15 MS (APCI) 482 (M+H⁺, 100%)

e) [1S-(1α,2β,3β,4α)]-2-[[6-[7-(Butylamino)-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]oxy]acetic acid, 1,1-dimethylethyl ester

20 A mixture of the product from step (d) (0.15g) and *n*-butylamine (5ml) in 1,4-dioxane (10ml) was stirred at room temperature for 1 hour, concentrated and purified (SiO₂, ethyl acetate: hexane 1:5 as eluant) to give the subtitle compound (0.14g).

MS (APCI) 537 (M+H⁺, 100%)

25 **f) [1S-(1α,2β,3β,4α)]-2-[[4-[7-(Butylamino)-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-2,3-dihydroxycyclopentyl]oxy]acetic acid**

The product was prepared according to the method of example 1 step (g) using the product of step (e).

MS (ESI) 441 (M+H⁺, 100%)

30 NMR δH (d₆-DMSO) 9.01 and 8.63 (1H, t, rotamers), 4.94 (1H, q), 4.53 (1H, m), 4.04 (2H, m), 4.00 (1H, m), 3.85 (1H, m), 3.90 and 3.50 (2H, q, rotamers), 3.08 (2H, m), 2.64 (1H, m), 2.08 (1H, m), 1.65 (4H, m), 1.34 (2H, m), 0.99 (3H, t), 0.91 (3H, t).

Example 5

35 **[1S-(1α,2β,3β,4α)]-2-[[4-[7-(Butylamino)-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-2,3-dihydroxycyclopentyl]oxy]acetamide**

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To a solution of the product of example 4 (0.21g) in *N,N*-dimethylformamide (25ml) was added a solution of ammonia in acetonitrile (5ml) and bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (0.35g). The mixture was stirred for 10 minutes and *N,N*-diisopropylethylamine (300µl) was added. The reaction mixture was stirred at room temperature for 2 hours, concentrated and purified (Sep-pak® C18 silica, water to acetonitrile gradient elution followed by HPLC, Nova-pak® C18 column, 0.1% aqueous trifluoroacetic acid:acetonitrile 50:50) to give the title compound (0.09g).

MS (APCI) 440 ($M+H^+$, 100%)

NMR δ H (d_6 -DMSO) 8.99 (1H, t), 7.33 (1H, br s), 7.18 (1H, br s), 5.20-5.10 (2H, br s), 4.95 (1H, q), 4.57-4.53 (1H, m), 4.04-4.02 (1H, m), 3.88 (2H, s), 3.81-3.79 (1H, m), 3.49 (2H, q), 3.11-3.06 (2H, m), 2.70-2.60 and 2.15-2.01 (1H, m), 1.70 (2H, sextet), 1.63 (2H, quintet), 1.34 (2H, sextet), 0.99 (3H, t), 0.91 (3H, t).

Pharmacological data

The preparation for the assay of the P_{2T} -receptor agonist/antagonist activity in washed human platelets for the compounds of the invention was carried out as follows.

Human venous blood (100 ml) was divided equally between 3 tubes, each containing 3.2% trisodium citrate (4 ml) as anti-coagulant. The tubes were centrifuged for 15 minutes at 240G to obtain a platelet-rich plasma (PRP) to which 300 ng/ml prostacyclin was added to stabilize the platelets during the washing procedure. Red cell free PRP was obtained by centrifugation for 10 minutes at 125G followed by further centrifugation for 15 minutes at 640G. The supernatant was discarded and the platelet pellet resuspended in modified, Calcium Free Tyrode solution (10 ml) (CFT), composition: NaCl 137mM, $NaHCO_3$ 11.9mM, NaH_2PO_4 0.4mM, KCl 2.7 mM, $MgCl_2$ 1.1 mM, dextrose 5.6 mM, gassed with 95% O_2 /5% CO_2 and maintained at 37°C. Following addition of a further 300 ng/ml PGI_2 , the pooled suspension was centrifuged once more for 15 minutes at 640G. The supernatant was discarded and the platelets resuspended initially in 10 ml CFT with further CFT added to adjust the final platelet count to 2×10^5 /ml. This final suspension was stored in a 60 ml syringe at 3°C with air excluded. To allow recovery from PGI_2 -inhibition of normal function, platelets were used in aggregation studies no sooner than 2 hours after final resuspension.

In all studies, 3 ml aliquots of platelet suspension were added to tubes containing CaCl_2 solution (60 μl of 50 mM solution with a final concentration of 1mM). Human fibrinogen (Sigma, F 4883) and 8-sulphophenyltheophylline (8-SPT which was used to block any P_1 -agonist activity of compounds) were added to give final concentrations of 0.2 mg/ml (60 μl of 10 mg/ml solution of clottable protein in saline) and 300 nM (10 μl of 15 mM solution in 6% glucose), respectively. Platelets or buffer as appropriate were added in a volume of 150 μl to the individual wells of a 96 well plate. All measurements were made in triplicate in platelets from each donor.

The agonist/antagonist potency was assessed as follows.

Aggregation responses in 96 well plates were measured using the change in absorbance given by the plate reader at 660 nm. Either a Bio-Tec Ceres 900C or a Dynatech MRX were used as the plate reader.

15

The absorbance of each well in the plate was read at 660 nm to establish a baseline figure. Saline or the appropriate solution of test compound was added to each well in a volume of 10 μl to give a final concentration of 0, 0.01, 0.1, 1, 10 or 100 mM. The plate was then shaken for 5 min on an orbital shaker on setting 10 and the absorbance read at 660 nm.

20

Aggregation at this point was indicative of agonist activity of the test compound. Saline or ADP (30 mM; 10 μl of 450 mM) was then added to each well and the plate shaken for a further 5 min before reading the absorbance again at 660 nm.

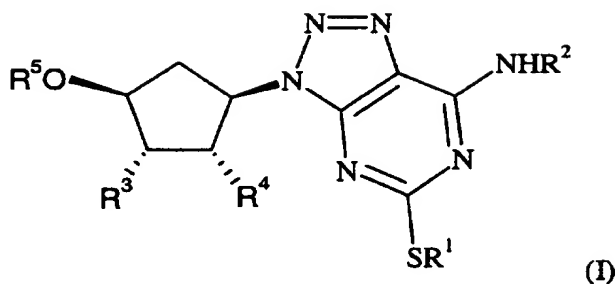
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Antagonist potency was estimated as a % inhibition of the control ADP response to obtain an IC_{50} . Compounds of the invention have pIC_{50} values of more than 5.0

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Claims

1. A compound of formula (I)



wherein:

R^1 is a C_{1-6} alkyl, C_{3-8} -cycloalkyl or a phenyl group, each group being optionally substituted by one or more substituents selected from halogen, OR^8 , NR^9R^{10} , SR^{11} or

C_{1-6} alkyl (itself optionally substituted by one or more halogen atoms);

R^2 is C_{1-8} alkyl optionally substituted by one or more substituents selected from halogen, OR^8 , NR^9R^{10} , SR^{11} , C_{3-8} -cycloalkyl, aryl (optionally substituted by one or more alkyl groups and/or halogen atoms), or C_{1-6} -alkyl; or R^2 is a C_{3-8} -cycloalkyl group optionally substituted by one or more substituents selected from halogen, OR^8 , NR^9R^{10} , SR^{11} ,

C_{1-6} -alkyl or phenyl (the latter two groups being optionally substituted by one or more substituents selected from halogen, NO_2 , $C(O)R^8$, OR^8 , SR^{11} , $NR^{12}R^{13}$, phenyl and C_{1-6} -alkyl which is optionally substituted by one or more halogen atoms);

one of R^3 and R^4 is hydroxy and the other is hydrogen, hydroxy or NR^9R^{10} ;

R^5 is hydrogen, C_{1-6} alkyl or $(CH_2)_nR^{14}$ where n is 1 to 3 and R^{14} is $COOH$, OR^{15} , $NR^{16}R^{17}$ or $CONR^{16}R^{17}$;

R^8 , R^9 , R^{10} and R^{11} are independently hydrogen or C_{1-6} alkyl;

R^{12} and R^{13} are independently hydrogen, C_{1-6} alkyl or acyl groups;

R^{15} , R^{16} and R^{17} are independently hydrogen or C_{1-6} alkyl; and

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 in which R^1 is C_{1-8} alkyl.

3. A compound according to claim 1 or 2 in which R^2 is C_{1-6} alkyl or a C_{3-8} -cycloalkyl group optionally substituted phenyl

4. A compound according to any one of claims 1 to 3 in which R^3 and R^4 are both hydroxy.

5. A compound according to any one of claims 1 to 5 in which R^5 is hydrogen or CH_2R^{12} where R^{12} is $COOH$ or $CONH_2$.

6. A compound according to claims 1 which is:

[1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-4-[7-[(2-Phenylcyclopropyl)amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-cyclopentane-1,2,3-triol,

[1S-[1 α ,3 β ,4 α (1S*,2R*)]]-2-[3-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-cyclopentyloxy]acetic acid,

[1S-[1 α ,2 β ,4 α (1S*,2R*)]]-2-[[2-Hydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-cyclopentyl]oxy]acetic acid,

[1S-(1 α ,2 β ,3 β ,4 α)]-2-[[4-[7-(Butylamino)-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-2,3-dihydroxycyclopentyl]oxy]acetic acid,

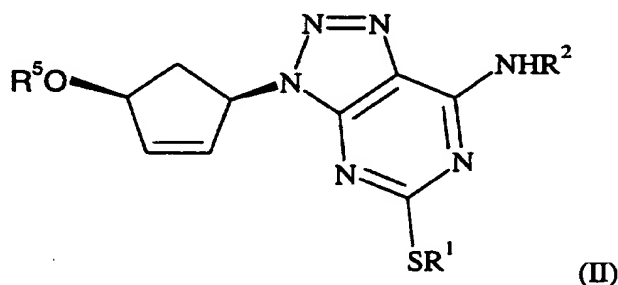
[1S-(1 α ,2 β ,3 β ,4 α)]-2-[[4-[7-(Butylamino)-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-2,3-dihydroxycyclopentyl]oxy]acetamide,

or a pharmaceutically acceptable salt or solvate thereof.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 in combination with a pharmaceutically acceptable diluent, adjuvant or carrier.

8. A compound according to any one of claims 1 to 6 for use in therapy.

9. A process for the preparation of a compound of formula (I) which comprises; hydroxylation of a compound of formula (II):



where R^1 , R^2 and R^5 are as defined in formula (I) or are protected derivatives thereof,

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and optionally thereafter in any order:

- converting one or more functional groups into a further functional groups
- removing any protecting groups
- forming a pharmaceutically acceptable salt or solvate.

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ABSTRACT

The invention provides new triazolo[4,5-*d*]pyrimidine compounds, their use as medicaments, compositions containing them and processes for their preparation.

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